Is methotrexate plus cyclosporine A a useful salvage therapy for rheumatoid arthritis patients unresponsive to other types of methotrexate combination treatment ?

Sirs,

Methotrexate (MTX) is considered to be the agent of first choice for rheumatoid arthritis of moderate or high activity (1). But acceptable suppression of disease activity is achieved in no more than 70% of patients on MTX monotherapy and the percentage is even lower at the severe end of the disease spectrum (1). Combination regimens consisting of methotrexate (MTX), salazosulfapyridine (SSZ) and/or hydroxychloroquine (HCO) are being increasingly used in these poor responders, but a sizable proportion of the patients remain still active (2, 3). MTX plus cyclosporin A (CSA) is a further combination regimen with a proven additive effect (4-6). We therefore examined, in an observational study, whether MTX+CSA can serve as salvage therapy for patients unresponsive to other MTX combinations.

From 1997 through 1998, we recruited 55 consecutive patients with RA (7) and persistent disease activity despite combination treatment with either MTX+SSZ+HCO (n=26), MTX+SSZ (n=13) or MTX+HCO (n=16). These were 37 females and 18 males, median age 58.7 years [interquartile range 55.2-64.01 years], disease duration 8.1 years [4.0-14.7], and Larsen grade 3 [2-4]; 41 were rheumatoid factor positive (8). For maximal efficacy and an optimal efficacy/tolerability ratio, the patients received MTX intravenously and the dose was adjusted individually. This resulted in a median 22.5 mg/week [22.5-25]. Doses were 2000 mg/day [2000-2000] for SSZ and 400 mg/day [400-400] for HCO. At inclusion in this study, MTX remained unchanged, and SSZ and HCO were terminated. CSA was initiated with 2.5 mg/kg/ day and escalated to 3.5 and 4.5 mg/kg/day, if necessary. Contraindications for CSA conformed with established guidelines (9). Arterial hypertension was required to be controlled with no more than two drugs. Newly developing or exacerbating hypertension was met by:1. reduction of CSA dose by 30-50%; 2. single-agent antihypertensive treatment; and, if the hypertension persisted, by 3. withdrawal of CSA. An increase in serum creatinine by 30% or above the upper limit of normal was addressed by reduction of CSA by 30-50%. If levels remained elevated, CSA was withdrawn. Prednisolone was tapered to the lowest effective dose. No nonsteroidal antiinflammatory agents were allowed.

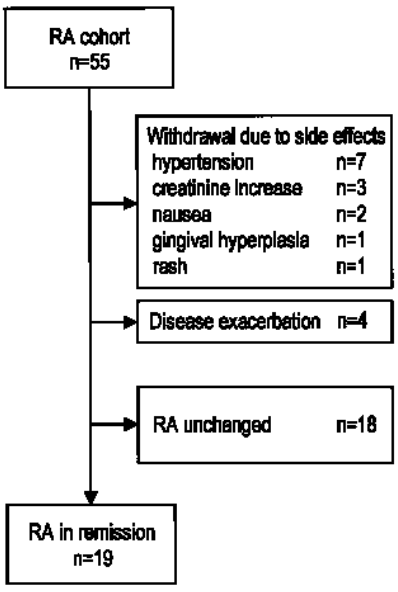

Fig. 1. Outcome of methotrexate plus cyclosporin A treatment.

Eighteen patients (33%) terminated MTX + CSA during the first year (Fig. 1). Four patients had a severe disease exacerbation. Seven patients developed hypertension prohibiting further CSA treatment. Three patients developed renal insufficiency and 4 patients terminated CSA because of either nausea, gingival hyperplasia or a rash. Deteriorating renal function and newly developing or exacerbating arterial hypertension were thus the main limiting side effects. These occurred in 5 of the 12 patients with, but in only 7 of the 43 patients without, preexisting hypertension ($p = 0.030$).

Thirty-seven patients stayed on MTX+CSA for at least 12 months, the median CSA dose being 3.2 mg/kg/day [2.5-4.0]. The prednisolone requirement dropped from 7.5 mg/day [5.0-10.0] to 4.0 mg/day [3.0-5.5] ($p < 0.001$). Since this was a cohort with particularly aggressive disease, our minimum requirement for a sufficient treatment response was the arrest of radiologic progression together with regression of the joint count and the C-reactive protein by at least 30%. This was attained in 19 of the 55 patients (34%), whereas MTX+CSA was either only marginally superior or equivalent to combinations of MTX, SSZ and HQ in the remaining 18 patients (33%).

In conclusion, these patients with RA refractory to combinations of MTX,SSZ and/ or HQ experienced a substantial number of CSA side effects. Hypertensive patients were particularly poor candidates for the combination of MTX+CSA, even if their blood pressure was previously well controlled. On the other hand 19 patients (34%) experienced a definitive benefit from this treatment, with the arrest of further radiological progression and regression of inflammatory activity. MTX+CSA is thus a viable option in patients refractory to other MTX combinations and should be included in future studies aimed at devising a rational approach to this highly selected patient subset.

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